Review Article

Natural killer cell biology and its effect on graft versus host disease

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Received: 13 September, 2017; Accepted: 16 November, 2017

Abstract

Natural killer (NK) cells were originally described in terms of their function. NK cells are of lymphoid origin and are found in the peripheral blood, spleen, and bone marrow, as well as other tissues. These cells are large, radio-resistant and granular lymphocytes that represent an important arm of innate immunity and are thought to play a critical role in the immune surveillance against tumors and virally infected cells. Allogeneic bone marrow transplantation (BMT) has proven to be an effective treatment for hematologic malignancies and some solid tumors. One of the major challenges of allo-stem cell transplantation (SCT) is to reduce the incidence and severity of GVHD while boosting the graft-versus-leukemia (GVL) effect. In the setting of allo-SCT, the reconstitution of NK cells is of notable interest due to their known capability to induce GVL without GVHD. Clinical applications of NK cells have been inspired by recognition of their potent anticancer activity. These studies discussed a solid basis for development of future NK cell trials for cancer therapy by minimizing risks and toxicities.

Keywords: Natural killer cell, bone marrow transplantation, graft versus host disease,graft versus leukemia

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Please cite this article as: Akhavan Rahnama M, Soleimani M, Moradi N, Soufi Zomorrod M. Natural killer cell biology and its effect on graft versus host disease. Arch Med Lab Sci. 2017;3(4):34-42.

Natural killer Cell Biology and Receptors

In 1971 Natural killer (NK) cells were originally described in terms of their function. NK cells are of lymphoid origin and are found in the peripheral blood, spleen, and BM, as well as other tissues. These cells are large, radio-resistant and granular lymphocytes that represent an important arm of innate immunity and are thought to play a critical role in the immune surveillance against tumors and virally infected cells(1).

Two major subsets of NK cells are found in human subjects that can be distinguished by their levels of CD56 expression, namely CD56dim and CD56bright(2). CD56dim NK cells are fully mature, make up approximately 90% of the NK cells in peripheral blood, and predominantly mediate cytotoxicity responses. In contrast, CD56bright cells are more immature, make up approximately 5% to 15% of total NK cells, and have been considered primarily as cytokine producers while playing a limited role in cytolytic responses(3).

NK cells are regulated by a number of receptors with opposite function that finely tune potent effector functions such as cytolytic activity; through the perforin/granzyme-dependent pathway and use of Fas ligand (FasL) and tumor necrosis factor related apoptosis inducing ligand (TRAIL) to kill target cells; and production of cytokines playing a key role in inflammation and regulation of both innate and adaptive immune responses(4, 5). So cytokines play a major role in the differentiation (IL-15, fms-like tyrosine kinase 3(flt3) ligand, stem cell factor(SCF), fetal liver kinase ligand(flk2L)) and in the function (IL-2, IL-15, IL-18, IL-21 and IFN-α/β) of NK cells(6, 7).

Generally NK cells have 5 main categories of

cell surface receptors. Activating receptors (e.g. CD16, NKp46, NKG2D, NKG2C, KIR-S, Ly9), inhibitory receptors (e.g. KIR-L, NKG2A), chemotactic receptors (e.g. CCR2, CCR5, CXCR1, CXCR4, CXCR6), cytokine receptors(e.g. IL-1R, IL-15R, IL-18R), adhesion receptors(e.g. β1 integrins) (8).To explain more about the receptors of this intrinsic immune cell, here is a brief summary about them: An important category of receptors in the NK cells are the killer cell Ig-like receptors (KIRs) which specifically recognize groups of HLA-C, HLA-B and HLA-A alleles (9, 10).

Another class of MHC class I-specific receptors is comprised of the C-type lectin molecule CD94, which is covalently associated with a member of the NKG2 family. Like KIR receptors, these receptors have been also shown to exert inhibitory (NKG2A or NKG2B) or activating (NKG2C) signals upon binding non-classical HLA-E molecules on human targets (11). NK cells also have Ig-like transcript (ILT) receptors that interact with HLA-G (to protect the fetus and placenta from rejection (12). Another group of NK cell receptors comes from a more diverse family of receptors of NK-cell-specific Ig-like molecules that are known as natural cytotoxicity receptors, or NCRs. NCRs include NKp30, NKp46, and NKp44 as well as NKG2D. NKG2D is a member of the NKG2 family expressed by NK cells and cytotoxic lymphocytes (CTLs) (13, 14).Most NK cells can express the FcγRIII (CD16) molecule, which recognizes the Fc component of bound Ig molecules and initiates cytolysis by the antibody dependent cellular cytotoxicity (ADCC) pathway, thus giving the NK cell another method of target recognition(10, 15)

Recently, NK cells were officially classified as the prototypical members of the group 1 innate lymphoid cells (ILCs), which are defined by their capacity to secrete IFN-Ɣ but not type 2 cytokines (IL-4 and IL-13), IL-17, or IL-22 (16). Human NK cells are classically defined as CD56+CD3- cells, distinguishing them from CD56+CD3+ cells, which consist of a mixed population of NK-like T cells and antigen-experienced T cells that have upregulated several NK cell markers(17).

Natural killer Cell and GVHD

Allogeneic bone marrow transplantation (BMT) has proven to be an effective treatment for hematologic malignancies and some solid tumors(18). However, the high incidence of graft-versus-host disease (GVHD) as a complication of this treatment has limited the overall effectiveness of BMT. GVHD is mediated by the activation and proliferation of alloreactive T cells and causes tissue damage in the host, primarily in the gastrointestinal tract, liver, and skin causing significant morbidity and mortality.

One of the major challenges of allo-Stem Cell Transplantation (SCT) is to reduce the incidence and severity of GVHD while boosting the graft-versus-leukemia (GVL) effect. In the setting of allo-SCT, the reconstitution of natural killer (NK) cells is of notable interest due to their known capability to induce GVL without GVHD. Studies of the role of NK cells in bone marrow engraftment demonstrated that host NK cells persisting after conditioning can contribute to graft rejection while donor NK cells can promote hematopoietic engraftment.

The first study suggesting a relationship between NK cells and GvHD development was reported by Lopez and coworkers from the Sloan Kettering Cancer Center. They showed a significant association between GvHD development and pre-transplant levels of NK cell activity, as measured by cytotoxic assays performed using herpes simplex virus type 1-infected fibroblast as target cells, in peripheral blood of a small and heterogeneous cohort of 13 patients undergoing different protocols of HCT(19). In 2015 Jacobs B. and et al could demonstrate that NK cells gain cytotoxic and cytokine producing functions early during hematopoietic immune reconstitution following autologous SCT.(5) In addition to clinical studies, it has been shown in animal models that IL-2-activated NK cells may efficiently prevent or even reduce GVHD without any adverse impact on their important GVL effect (20).

After chemotherapy or hematopoietic stem cell transplantation, NK cells are the first lymphoid cells to recover(21). Surprisingly, such post grafting regeneration of NK cells does not cause clinical graft-versus-host disease (GVHD); this has led to the conclusion that normal nonhematopoietic tissues lack ligands able to activate NK cell lysis(22).

The concept of an NK-mediated regulatory function is also supported by the observation that a higher number of bone marrow NK cells has been associated with a decreased incidence of chronic GVHD after HLA identical sibling bone marrow transplants in human(23). Researches in 2002 and 2004 showed that this regulatory function can be indirect, through the interplay and molecular crosstalk with dendritic cells (DCs) (24, 25). On the one hand, DCs can prime, further the activation of, augment the expansion of, and enhance the activities of NK cells through the production of cytokines such as IL-2, IL-12, IL-15, IFN-a/b, and TNFa(26).The regulatory function of NK cells on adaptive immune responses appears also to be mediated through direct lysis of activated T cells(27, 28).This pathway has been postulated to play an important role in the generation of memory T cell repertoire. Several recent observations suggest that certain subpopulations of NK cells promote allograft tolerance via a cytolysis-dependent regulatory pathway(29). However, little is known about the effects of NK cells on donor T cells after BMT. In 2010, it was shown that NK cells can regulate chronic GVHD by limiting recipient minor histocompatibility Ag (mHA)-driven proliferation of donor CD4+ T cells(30).

According to studies by scientists, the relationship between NK cell and GVHD can be generally described in two ways: firstly, NK Cell cytotoxic functions and GvHD prevention: NK cells can suppress GvHD development through their cytotoxic function either directly, by depleting activated alloreactive T cells, or indirectly, by depleting APC and preventing T cell stimulation cell killing by NK cells appears to be dependent on both perforin production and FAS-mediated induction of apoptosis, and secondary NK cell cytokine production and GvHD induction, Although it is unclear if NK cells production of immunesuppressive cytokines can prevent GvHD(4, 31),it is established that pro-inflammatory cytokine production by NK cells can contribute to GvHD development(32).In a xenogeneic model, Xun et al. showed that in vitro interleukin-2 (IL-2)-activated human NK cells producing interferon-γ(IFN-γ) and tumor necrosis factor-α(TNF-α) were able to induce acute GVHD upon transfer into SCID mice .What is now important about NK cells and its impact on GVHD is that researchers are looking for new ways to reduce GVHD with the help of these cells, which we will continue to mention these activities(33).

Natural Killer Cell Memory

The ability of the immune system to respond rapidly and provide enhanced protection of the host against a previously encountered pathogen is defined classically as immunological memory. Immunological memory is a cardinal feature of adaptive immunity. Although NK cells have long been considered short-lived innate lymphocytes that respond rapidly to transformed and virus-infected cells without prior sensitization, it has recently become appreciated that NK cells can also acquire functional qualities commonly associated with immunological memory similar to that of T and B cells in response to pathogens and in non-infectious settings(34).

Antigen-specific memory NK cell responses were first observed in a murine model of hapten-induced CHS(35).

Long lived memory cells are generated after initial infection and display heightened responses upon secondary challenge with the same pathogen. The process of memory formation in T cells has been well studied and is generally divided into three distinct phases. Upon exposure to cognate antigen, naive CD8+ T cells clonally expand and differentiate into effector cells during the ‘‘expansion’’ phase. This first phase is followed by a rapid ‘‘contraction’’ phase, when the vast majority of effector CD8+ T cells undergo apoptosis to form a small, but stable, pool of surviving cells that then enter the third ‘‘memory’’ phase. Memory CD8+ T cells persist throughout the host organs and maintain their longevity through self-renewal until a subsequent encounter with their cognate antigen, when they exhibit enhanced effector function and host protection. In an experimental system in which Ly49H+ NK cells were adoptively transferred into mice lacking this receptor, these Ly49H+ cells underwent robust antigen-driven expansion after MCMV infection. Similar to activated CD4+ T cells, expanded effector NK cells undergo a slower and sustained contraction phase to establish a long-lived and self-renewing ‘‘memory’’ pool of antigen-specific NK cells that can be recovered many

months after infection in a variety of peripheral tissues(36).

CAR modified Natural killer cells

Recent years have seen remarkable advances in field of engineering of immune cells as cancer therapy. Whereas chimeric antigen receptors (CARs) have been used comprehensively to convey the specificity of autologous T cells against hematological malignancies with remarkable clinical results, studies of CAR-modified natural killer cells have been generally in preclinical phases(37). NK cells for adoptive therapy can be derived from several different sources which is explained in other parts. Allogeneic NK cells can be generated from the peripheral blood of healthy donors or expanded from umbilical cord blood. Regardless of the source, there are several features of expanded, activated CB, or PB-derived NK cells that make them useful effectors for gene modification.

With CAR-modified primary human NK cells can be effector modified immune cells against a number of hematologic and solid tumor antigens, including CD19, CD20, GD2, and HER-2(38-40). While non-viral expression techniques such as nucleofection or electroporation can produce robust CAR-mediated killing, the short-lived nature of these CAR molecules would likely dictate the need for repeated infusions in the clinical setting(41).

NKG2D Receptor

Expanded, activated NK cells generally express a wide range of activating receptors, including CD16, NKG2D, and the NCRs (NKp44 and NKp46), in spite of donor-to-donor variability(42, 43). These activated NK cells are prepared with KIRs and are "licensed to kill." In vivo expansion and persistence capacity of NK cells is clearly associated with antitumor activity in trials involving hematologic malignancies such as AML(44, 45). Moreover, ex vivo expanded primary human NK cells produce a different storm of cytokines more than T cells, including interferon (IFN)-g, IL-3, and granulocyte macrophage colony-stimulating factor (GM CSF), which may be associated with a lower risk of CRS(cytokine released syndrome)

While normal NK cell counts are usually detected within the first month after alloSCT regardless of the graft source, several months are required to acquire the immunophenotypic and functional characteristics of NK cells found in healthy donors. Rebuilding NK cells display a more immature phenotype expressing the inhibitory natural killer group two A (NKG2A) receptor at around 90% compared to around 50% in healthy donors. During the NK development and peripheral maturation, the CD56dim NK cells lose NKG2A expression but up-regulate the expression of the activating NKG2C receptor, killer cell inhibitory immunoglobulin-like receptors (KIRs) and CD57(46). The allo reactivity of NK cells is determined by various receptors including the activating CD94/NKG2C and the inhibitory CD94/NKG2A receptors, which both recognize the non-classical human leukocyte antigen E (HLA-E. studies have shown that NK cells expressing the activating CD94/NKG2C receptor are significantly reduced in patients after alloSCT with severe acute and chronic graft-versus-host disease (GvHD). Moreover, the ratio of CD94/NKG2C to CD94/NKG2A was reduced in patients with severe acute and chronic GvHD after receiving an HLA-mismatched graft. Collectively, these results provide evidence for the first time that CD94/NKG2C is involved in GvHD prevention(12).

IL2 and LAK cells, a key for more and powerful NK cells

At the University of Minnesota, researchers first confirmed the daily use of low dose IL-2 to expand NK cells after autologous HSCT in patients with non-Hodgkin lymphoma and breast cancer. Later, they activated autologous NK cells ex vivo with IL-2 for 24 hours, infused them into patients and administered subcutaneous IL-2 on daily basis .While autologous NK cell studies showed limited efficacy, they did yield important findings: 1).IL-2 can be administered safely at daily or 3 times weekly intervals, 2) IL-2 can induce an increase in circulating cytotoxic lymphocytes with a disproportionate increase in NK cells(47).

In innovative studies at the NCI, Rosenberg and colleagues infused melanoma and renal cell carcinoma

patients with autologous peripheral blood cells treated ex vivo with IL-2. The product was enriched with NK cells and named "lymphocyte activated killer" (LAK) cells. High dose IL-2 was administered to patients after LAK infusions to promote their in vivo persistence and activity. In a subsequent trial, the NCI group adoptively transferred in vitro expanded autologous tumor-infiltrating lymphocytes (TILs) to patients with metastatic melanoma(48). These studies and others have revealed important new knowledge: 1) high-dose IL-2 used in vivo with the goal of activating NK cells has significant but manageable toxicity owing to severe capillary leak syndrome, whereas low-dose subcutaneous IL-2 was well tolerated, 2) lymphodepleting chemotherapy using high-dose cyclophosphamide and fludarabine facilitated in vivo expansion of autologous adoptively transferred cytotoxic T lymphocytes and led to enhanced efficacy,3) chemotherapy induces lymphopenia, changes the competitive balance between transferred lymphocytes and endogenous lymphocytes, changes the cytokine milieu and depletes inhibitory cell populations (T regulatory cells [Tregs])(49).

MSC and Natural killer cell therapy

Bone-marrow-derived MSCs (BM-MSCs) can inhibit NK cell proliferation, cytotoxicity, and cytokine production by secreting IDO1, TGFb, HLA-G, and PGE2(50, 51).However, they can be also lysed by activated NK cells, depending on their expression of activating NK receptor ligands, including MHC class I polypeptide-related sequence (MICA, B), UL16 binding proteins (ULBPs), CD112, and CD155.

Mesenchymal stem cells (MSCs) show pleiotropic factors with immunosuppressive activity involved in cancer progression(52, 53). This is observed that T cell derived MSCs were more powerfully immunosuppressive than NK-MSCs and affected both NK function and phenotype by CD56 expression. T-MSCs shifted NK cells toward the CD56dim phenotype and differentially modulated CD56bright/dim subset functions. However MSCs affected both degranulation and activating receptor expression in the CD56dim subset, they mainly inhibited interferon-gamma production in the CD56bright subset. Pharmacological inhibition of prostaglandin E2 (PGE2) synthesis and, in some MSCs, interleukin-6 (IL-6) activity restored NK function, whereas NK cell stimulation by PGE2 alone mirrored T-MSC-mediated immunosuppression. Our observations provide insight into how stromal responses to cancer reduce NK cell activity in cancer progression[53].

The spectrum of MSC immunosuppressive activity in humans includes secretion of human leukocyte antigen (HLA-G), transforming growth factor b (TGFb), prostaglandin E2 (PGE2), tumor necrosis factor alpha-inducible protein 6 (TNFAIP6/ TSG-6), heme oxygenase 1 (HO-1/HMOX1), IL-10, IL-6, indoleamine 2,3-dioxygenase 1 (IDO1), hepatocyte growth factor (HGF), and leukemia inhibitory factor (LIF) as well as programmed death ligand (PD-L1/2) and Fas ligand (FasL) signaling(54-56).

The finding that MSCs could inhibit the expression of activating receptors on the surface of NK cells was indicative of a possible loss of cytotoxic activity known to involve engagement of causing receptors. To assess a possible MSC-mediated inhibitory effect on the lytic potential of NK cells, researchers did cytolytic assays in different NK-cell populations from different donors were used as effectors after short-term culture with 100 U/mL IL-2 either in the presence or in the absence of MSCs(57).

MSCs were originally shown to have strong inhibitory effect on T-cell activation and function. In recent years, inhibition has been also observed in dendritic cells (DCs), B cells, and NK cells. In this framework, researchers informed that MSCs can block the IL-2–induced proliferation of fresh peripheral blood NK cells. The use of MSCs may become a common approach in BM transplantation not only for their possible beneficial effect on the engraftment of hematopoietic stem cells, but also for their immunosuppressive potential. On the other hand, NK cells have been shown to play a central role in the successful outcome of haplo identical BM transplantation to treat AML.NK cells derived from the HSCs of the donor can exert a direct GVL effect, provided they express KIRs that do not recognize one

or more HLA class I alleles of the patient.

Recent studies reported that NK-MSC interactions not only provided strong MSC-mediated anti proliferative effect on NK cells but also verified that IL-2–activated NK cells can powerfully kill both allogeneic and autologous MSCs. The killing reflects the fact that MSCs are characterized by low levels of HLA class I antigens and also express several ligands recognized by activating NK receptors(58).

Future perspectives

1. Genetic modification and alternative sources of NK cell products

To overcome restrictions of the donor-derived NK cell therapies, several groups have investigated alternative donor sources including UCB, NK cell lines and pluripotent stem cells. If cryopreservation can be optimized, the quick availability of an off-the-shelf product denotes a significant step forward. Further advantages include the ability to perform preclinical testing and to select for donors based on favorable characteristics including optimal KIR-genotype(59).

2. UCB-derived NK cells

UCB progenitors provide a rich source of hematopoietic progenitor cells and serve as an important in vitro system for studying the development of human NK cells. Clinically appropriate doses of UCB-derived NK cells can be generated without the use of feeder cells in compare to NK cells derived from peripheral blood(59) . NK cells generated from UCB contain a mixture of immature and mature cells that produce cytokines and show cytotoxicity. Development of functional NK cells (e.g. CD34 isolation, in vitro expansion) takes up to 4 weeks and requires processing in a GMP facility. Studies are incomplete and preliminary data is insufficient to assess comparative advantages(60).

3. NK cell lines

Many research teams have explored the use of cell lines derived from malignant NK cell clones (NK-92, NKL, KYHG-1, YT, NKG) NK cell lines keep some level of direct cytotoxic function and usually lack expression of inhibitory KIR. Because they can be grown in culture, genetic modification with different cytokine genes or chimeric antigen receptors is easily accomplished. Among the lines, NK-92 cells remain the most established and have been tested in clinical trials that include patients with renal cell carcinoma and malignant hematological malignancies. . Because of their amenability to ex vivo manipulation, these cell lines may provide an important platform to facilitate whole-body in vivo imaging of infused cells. Appropriate technology remains to be developed(59).

4. NK cells derived from pluripotent stem cells

Pluripotent stem cells are as an available and additional source of NK cells. These include human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs). Novel methods of iPSC generation have approached 100% efficiency, thus bringing closer the day that hematopoietic-based therapies derived from these lines become available for clinical use. A defined method for producing NK cells from hESCs and iPSCs amenable to clinical translation has been recently established [62]. By adapting a feeder-free differentiation system, mature and functional NK cells can be generated in a system agreeable to clinical scale-up. Significantly, in contrast to UCB-CD34+ derived NK cells or NK cell lines, the iPSC-derived NK cells maintained high levels of KIR and CD16 expression. If KIR expression does indeed dictate acquisition of final effector function, some of the relative advantages of using iPSC-derived NK cells for anti-cancer therapies are clarified. Using this improved differentiation method, it is estimated that one 6-well plate of hESCs or iPSCs could provide enough NK cells to treat several patients at the PB-NK doses currently used. Other advantages are:

1) Unlimited source of KIR-typed NK cells for adoptive immunotherapy,

2) High level of function in preclinical animal models

3) A platform genetically responsive to modify the therapy based on the patient’s cancer via tumor-specific receptors (TCRs or CARs)(61).

At present, however, using iPSCs on a patient-specific basis is impossible. Third party iPSC-derived NK cells are subject to immune rejection in the recipient. To circumvent this limitation, specific genetic modulation must be used to decrease immunoreactivity of the infused cells(61).

Conclusion

Clinical applications of NK cells has been inspired by recognition of their potent anticancer activity. These studies discussed a solid basis for development of future NK cell trials for cancer therapy by minimizing risks and toxicities. Important questions remain to be answered, most urgently, determination of minimum in vivo NK cell expansion needed for effective anti-tumor activity in clinical approaches. At present, results involving NK cell expansion interventions remain capricious. Also, NK therapy for solid tumors is limited by uncertain homing which its mechanism is unknown and have autoimmune diseases by an immunosuppressive induced microenvironment that may interfere with immune responses. To improve and progress NK cell therapies, both further study of basic NK biology and a better understanding of interactions with other immune cells will be required. NK cell products characteristics and effective cytokine cocktails with optimal proportions will probably differ from different tumor types and patients. Targeting CD16 remains an attractive way to increase specificity, resembling of genetically modified T cells. Future clinical trials will be designed to exploit strategies to overcome the host immune barriers. In the same way, strategies to discover ex vivo NK cell expansion from blood, lymphoid progenitors, or other sources are being tested. In hematopoetic stem cell transplantation, future studies are evaluating donor NK cell immunogenetics.

Conflict of interest

We have no conflict of interest.

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